Remarks

Applicants request reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Upon entry of the amendments, claims 1-6 and 11-63 will remain pending in the application, with claims 23-27 and 32-52 being withdrawn from consideration. Claims 8-10 and 64 are presently being canceled. No claims are presently being added. Claims 1-6, 53, 55-29 and 61-63 are presently being amended. Exemplary support for the claim amendments exists at page 14, lines 3-4; page 10, line 1 through page 11, line 27; and page 21, lines 27-29.

II. Replacement Drawings

The Examiner maintained prior objections to the drawings, but the objections are now moot. Applicants submit herewith a complete set of replacement drawings that address all of the objections. Accordingly, Applicants request withdrawal of the objection.

III. Scope of the Invention

Applicants note the Examiner's comments concerning the scope of the invention in section 14 of the Office Action. The comments are not directly tied to a rejection, but allege that the specification's definition of "multiple toxicity associated domains" is inconsistent with the structure of the pending claims. In view of the foregoing amendments, however, the apparent inconsistency no longer exists.

IV. Claims 1-6 Are Definite

Claims 1 and 2-6 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. According to the rejection, one skilled in the art would not know how to number amino acids in the CH_2 domain, and therefore would be unable to locate the appropriate amino acids in a generic immunoglobulin. Numerous numbering schemes allegedly exist, and the application of each scheme to different classes of immunoglobulin molecules allegedly gives disparate results.

Applicants do not acquiesce in the rejection's propriety. Nevertheless, the foregoing amendments obviate the rejection. The amended claims recite that numbering should be done according to the Kabat scheme and that the immunoglobulin is an IgG immunoglobulin.

Because the indefiniteness rejection is now moot, Applicants request its withdrawal.

V. *Claims 1-6, 8-22 and 28-31 Are Enabled*

Claims 1-6, 8-22 and 28-31 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly violating the enablement requirement. According to the rejection, the amino acid numbering system is "critical or essential to the practice of the invention, but is not included in the claims." Numerous numbering schemes allegedly exist, and the application of each scheme to different classes of immunoglobulin molecules allegedly gives disparate results.

Applicants do not acquiesce in the rejection's propriety. Nevertheless, the foregoing amendments obviate the rejection. The amended claims recite that numbering should be done according to the Kabat scheme and that the immunoglobulin is an IgG immunoglobulin.

Because the enablement rejection is now moot, Applicants request its withdrawal.

VI. *Claims 53-64 Have Descriptive Support*

Claims 53-64 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly violating the written description requirement. According to the rejection, the specification and original claims are "supportive of a method for inhibiting BR96 (ATCC: HB10036) induced toxicity resulting from immunoglobulin immunotherapy," but not of a method for inhibiting "generic immunoglobulin-induced toxicity." Applicants traverse the rejection.

The rejection misconstrues the meaning of "inhibiting immunoglobulin-induced gastrointestinal toxicity" in claims 53-64. Contrary to the rejection, *inhibiting* immunoglobulin-induced gastrointestinal toxicity in the context of the present invention does not equate to treating symptoms of immunoglobulin-induced gastrointestinal toxicity generally. The inhibition achieved by the present invention results from administering a modified IgG1 immunoglobulin or Ig fusion protein, as opposed to administering an

unmodified IgG1 immunoglobulin or Ig fusion protein. Selecting an appropriately modified IgG1 immunoglobulin or Ig fusion protein for administration *inhibits* immunoglobulin-induced gastrointestinal toxicity because it retards or prevents the development of such toxicity.

Extensive support for *inhibiting* immunoglobulin-induced gastrointestinal toxicity in this manner exists throughout the specification. For example, the paragraph bridging pages 3-4 states that "[t]he present invention provides methods for inhibiting immunoglobulin-induced toxicity by using known immunoglobulin or Ig fusion protein molecules which are structurally altered in their constant regions so that the resulting structurally altered immunoglobulin or Ig fusion protein molecules exhibit reduced or inhibited toxicity in vivo compared to their original unmodified counterparts." Likewise, the last full paragraph on page 13 states that "[t]he present invention provides a method for inhibiting immunoglobulin-induced toxicity resulting from the use of immunoglobulin during therapy or in vivo diagnosis. For example, the methods of the invention would be useful to minimize the toxicity associated with prolonged clinical exposure to immunoglobulin use during or after tumor imaging with radiolabeled antibodies." Still further, the first paragraph on page 16 states that '[t]he invention further provides a method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject. The method comprises administering to the subject an antibody which has been modified so that at least a portion of the constant region has been structurally altered as discussed supra."

The specification also provides extensive guidance for making appropriate modifications to immunoglobulins or Ig fusion proteins. For example, pages 21-24 describe various modified molecules, pages 25-27 describe nucleic acids that encode modified molecules, and pages 28-33 & 38-49 describe methods of making modified molecules. These passages include several working examples.

Accordingly, the claimed invention is well supported by the specification and Applicants request withdrawal of the written description rejection.

VII. Claims 1-6, 8-22, 28-31 and 53-64 Are Enabled

Claims 1-6, 8-22, 28-31 and 53-64 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly violating the enablement requirement. According to the rejection, the specification "is not reasonably enabling for a method for 'inhibiting immunoglobulin-induced toxicity in a subject' or a method for 'inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject' comprising administering to said subject, via any route, a generic modified immunoglobulin (including IgG, IgM, IgA, and IgE) containing structurally altered multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH2 domain." In particular, the rejection states that "the instant specification merely demonstrates how to *avoid* inducing toxicity mediated by effector functions of the Fc receptor or complement-mediated toxicity in dogs by not 'treating' the dogs with a chimeric BR96, but treating with a CH2 domain-deleted chimeric BR96 antibody, or hBR96-2B that is structurally altered specifically at amino acid residues 235 and 237 in the CH2 domain of the constant region of BR96." Applicants traverse the rejection.

Like the written description rejection discussed above, this enablement rejection misconstrues the terms "inhibiting immunoglobulin-induced toxicity" and "inhibiting immunoglobulin-induced gastrointestinal toxicity." *Inhibiting* such toxicities does not "require[ ] that the subject to whom the modified immunoglobulin is administered has toxicity pre-induced by an immunoglobulin that is unmodified . . . , which immunoglobulin was administered to the subject prior to the administration of the modified immunoglobulin." Moreover, *inhibiting* immunoglobulin-induced toxicity in the context of the present invention does not equate to treating symptoms of immunoglobulin-induced toxicity generally. The inhibition achieved by the present invention results from administering a modified IgG1 immunoglobulin or Ig fusion protein, as opposed to administering an unmodified IgG1 immunoglobulin or Ig fusion protein. Selecting an appropriately modified IgG1 immunoglobulin or Ig fusion protein for administration *inhibits* immunoglobulin-induced toxicity because it retards or prevents the development of such toxicity.

This meaning of *inhibiting* immunoglobulin-induced toxicity is evident from the specification. For example, the paragraph bridging pages 3-4 states that "[t]he present invention provides methods for inhibiting immunoglobulin-induced toxicity by using known

immunoglobulin or Ig fusion protein molecules which are structurally altered in their constant regions so that the resulting structurally altered immunoglobulin or Ig fusion protein molecules exhibit reduced or inhibited toxicity in vivo compared to their original unmodified counterparts." Likewise, the last full paragraph on page 13 states that "[t]he present invention provides a method for inhibiting immunoglobulin-induced toxicity resulting from the use of immunoglobulin during therapy or in vivo diagnosis. For example, the methods of the invention would be useful to minimize the toxicity associated with prolonged clinical exposure to immunoglobulin use during or after tumor imaging with radiolabeled antibodies." Still further, the first paragraph on page 16 states that '[t]he invention further provides a method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject. The method comprises administering to the subject an antibody which has been modified so that at least a portion of the constant region has been structurally altered as discussed supra."

The claims *must* be read in view of the specification, of which they are a part. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 986 (Fed. Cir. 1995) (*en banc*), *aff'd*, 116 S. Ct. 1364 (1996). Indeed, "the specification is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips v. AWH Corporation*, 415 F.3d 1303, 1315 (Fed. Cir. 2005). In the present case, therefore, the claim terms "inhibiting immunoglobulin-induced toxicity in a subject" and "inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject" must be interpreted as retarding or preventing the development of such toxicity in immunoglobulin or Ig fusion protein therapy.

Applicants maintain that the claims, when properly construed, are enabled for all of the reasons set forth in this and prior responses. Accordingly, Applicants request withdrawal of the enablement rejection.

VIII. Claims 1-6, 8-22, 28-31 and 53-64 Are Definite

Claims 1-6, 8-22, 28-31 and 53-64 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. With regard to claims 53 and 59, the rejection alleged that structural alterations at amino acids 235 and 237 cannot constitute alteration of "multiple toxicity-associated regions" because those amino acids are within the same

toxicity-associated region. With regard to claims 54-58 and 60-64, the rejection alleged that it is "unclear how a gastrointestinal toxicity induced in a mammalian subject by any generic immunoglobulin or any IgG1 can be inhibited by administering [a modified IgG of the invention]." With regard to claims 1-22 and 28-31, the rejection alleged that "[i]t is unclear how administration of a modified generic immunoglobulin to a subject having toxicity induced (*i.e.*, preinduced) by an immunoglobulin specific to a disease target can inhibit the toxicity." Applicants traverse the rejection.

A. Claims 53 and 59 Are Definite

The rejection of claims 53 and 59 for referring to "multiple toxicity-associated regions" is moot in view of the foregoing amendments. The amended claims refer to one toxicity-associated region.

B. Claims 1-22, 28-31, 54-58 and 60-64 Are Definite

The rejection of claims 1-22, 28-31, 54-58 and 60-64 is based on an erroneous construction of what *inhibiting* immunoglobulin-induced toxicity means. As explained above, *inhibiting* immunoglobulin-induced toxicity in the context of the present invention does not equate to treating symptoms of immunoglobulin-induced gastrointestinal toxicity generally. The inhibition achieved by the present invention results from administering a modified IgG1 immunoglobulin or Ig fusion protein, as opposed to administering an unmodified IgG1 immunoglobulin or Ig fusion protein. Selecting an appropriately modified IgG1 immunoglobulin or Ig fusion protein for administration *inhibits* immunoglobulin-induced gastrointestinal toxicity because it retards or prevents the development of such toxicity.

Given this understanding of inhibiting immunoglobulin-induced toxicity, it is clear that the claims do not require a pre-induced toxicity and that the claimed method is not directed to treating immunoglobulin-induced toxicity generally. When properly construed, therefore, the claims are definite and clear for all of the reasons set forth in this and prior responses. Accordingly, Applicants request withdrawal of the indefiniteness rejection.

IX. Claims 1-2, 5, 8, 28-29, 53, 59 and 63 Are Novel

Claims 1-2, 5, 8, 28-29, 53, 59 and 63 were rejected under 35 U.S.C. § 102(a) for allegedly being anticipated by Slavin-Chiorini *et al.*, Cancer Res., 55: 5957s-5967s (1995)

("Slavin-Chiorini"). According to the rejection, Slavin-Chiorini reports administering CH2 domain-deleted antibodies to patients. Applicants traverse the rejection.

Immunoglobulins of the claimed invention have CH_2 domains, unlike the CH_2 domain-deleted antibodies of Slavin-Chiorini. For at least this reason, Slavin-Chiorini does not anticipate the claimed invention and Applicants request withdrawal of the anticipation rejection.

X. *Claims 1-6, 8, 11, 13-15, 17-19, 21-22, 28-31, 53, 55-59 and 61-63 Are Novel*

Claims 1-6, 8, 11, 13-15, 17-19, 21-22, 28-31, 53, 55-59 and 61-63 were rejected under 35 U.S.C. § 102(a) for allegedly being anticipated by U.S. Patent No. 6,020,145 ("Hellstrom"). According to the rejection, Hellstrom taught administering BR96 fragments and fusion proteins that lack a CH_2 domain to subjects. Applicants traverse the rejection.

Immunoglobulins and Ig fusion proteins of the claimed invention have CH_2 domains, unlike the antibody fragments of Hellstrom. For at least this reason, Hellstrom does not anticipate the claimed invention and Applicants request withdrawal of the anticipation rejection.

XI. *Claims 1, 5, 12, 16 and 20 are Novel*

Claims 1, 5, 12, 16 and 20 were rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 93/02702 ("Gundel"). According to the rejection, Gundel taught administering a CH_2 domain-deleted antibody fragment to subjects. Applicants traverse the rejection.

Immunoglobulins of the claimed invention have CH_2 domains, unlike the CH_2 domain-deleted antibody fragments of Gundel. For at least this reason, Gundel does not anticipate the claimed invention and Applicants request withdrawal of the anticipation rejection.

XII. *Concluding Remarks*

This application is now in condition for allowance, and Applicants respectfully request reconsideration of it. If the Examiner has any remaining questions or believes that an interview would further examination of the application, she is invited to telephone the undersigned attorney.

Although Applicants believe that no fees are due, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment associated with the filing of this paper to Deposit Account Number 19-3880. Furthermore, if any extension of time is required, Applicants hereby petition for such extension and request that any fee due for the extension be charged to Deposit Account Number 19-3880.

Respectfully submitted,

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